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# The role of cardiac testing with the 0/1-hour high-sensitivity cardiac troponin algorithm evaluating for acute myocardial infarction

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**Background** The role of cardiac testing in the 3 zones (rule-out, observation, and rule-in) of the 0/1-hour algorithm to evaluate for acute myocardial infarction (AMI) has not been well studied. This study evaluated the 0/1-hour algorithm with a high-sensitivity cardiac troponin (hs-cTnI) assay and investigated cardiac testing in the 3 zones.

**Methods** Patients (n = 552) at a single urban center were enrolled if they were evaluated for AMI. Blood samples were obtained at presentation, 1 hour, and 3 hours for hs-cTnI. Follow-up at 30 to 45 days for death/AMI was done. The results of echocardiograms, stress testing, and coronary angiography were recorded.

**Results** In total, 45 (8.2%) had AMI (27 Type 1 and 18 Type 2) during the index hospitalization while at follow-up death/AMI occurred in 11 (2.0%) of patients. The rule-out algorithm had a negative predictive value for AMI of 99.6% while the rule-in zone had a positive predictive value of 56.6%. The MACE rate at follow-up was 0.4% for those in the rule-out group. There were 6/95 (6.3%) abnormal stress tests in the rule-out zone and 4 of these were false positives.

**Conclusions** The 0/1-hour algorithm had high diagnostic sensitivity and negative predictive value for AMI, and adverse events were very low in patients in the rule-out zone. Noninvasive testing in rule-out zone patients had low diagnostic yield. (Am Heart J 2021;233:68–77.)

There are approximately 8 to 10 million people evaluated annually in emergency departments (EDs) in the United States for possible acute myocardial infarction (AMI).[1] However, of these individuals 85% are ultimately not diagnosed with an AMI.[2-4] Much time and effort are spent evaluating these individuals with electrocardiograms (ECGs), cardiac markers, and noninvasive cardiac testing such as stress testing or coronary computed tomography angiography (CCTA). The annual cost of these evaluations in the United States is estimated at $5 to 10 billion.[5] Prolonged stays in the ED of these patients can lead to overcrowding, which has been associated with worse clinical outcomes.[6,7] Guidelines from the United States recommend that cardiac troponin (cTn) be measured over 3 to 6 hours in the evaluation of possible AMI.[8] However, studies done mostly out of the United States using high sensitivity cTn (hs-cTn) suggest that AMI can be excluded at presentation or over 1 hour utilizing accelerated diagnostic protocols.

Multiple studies have shown that AMI can be excluded at presentation when hs-cTn values are below the level of detection with a negative predictive value (NPV) of 99.1% to 100%.[9-12] In addition, there are studies demonstrating that a 0/1-hour algorithm looking at absolute changes in hs-cTn to exclude AMI has a similar high NPV.[13-15] The 0/1-hour algorithm divides patients into rule-out, observation, and rule-in zones. Both of these strategies utilize values that are substantially below the recommended 99th percentile cutoff value that is used in the definition of AMI.[16] The use of the 0/1-hour algorithm for the evaluation of possible AMI is recommended by the European Society of Cardiology.[17,18] Most of these studies, however, only included patients with chest pain and have excluded patients with significant renal insufficiency.[13]

The purpose of this study involving the 0/1-hour algorithm was 3-fold: first, validate a 0/1-hour algorithm with

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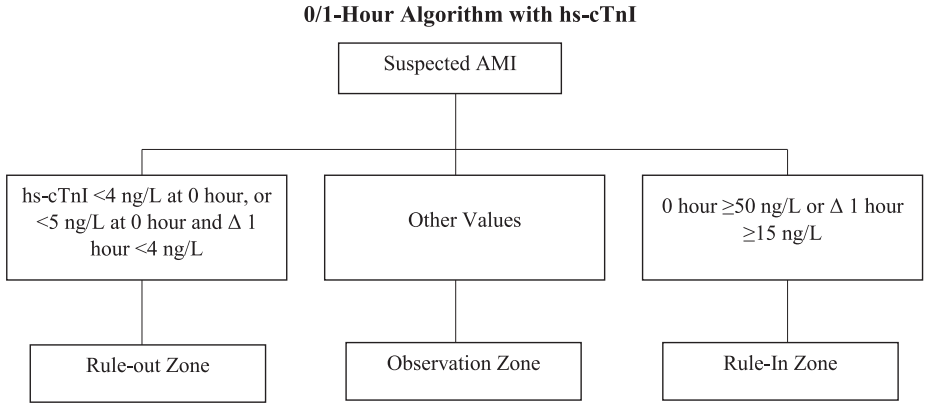
**Figure 1**




AMI, acute myocardial infarction; hs-cTnI, high sensitivity cardiac troponin I.

an hs-cTnI assay in a US cohort that has only been studied in one European trial up to this point[19]; second, explore the diagnostic utility of cardiac testing (echocardiogram, stress testing and coronary angiography) in the 3 zones of the algorithm; third, evaluate Type 1 and Type 2 AMIs in the context of the 3 zones of the algorithm.

## Methods

This was a substudy of the Rapid Evaluation of ACuTe Myocardial InfarctiON in the US (REACTION-US) trial. Details of the study have previously been published.[20] Briefly this was a prospective observational study that evaluated ED patients who had symptoms suspicious for an AMI. Inclusion criteria required patients age 21 years of age or older with an ECG and at least 1 cTnI ordered by the responsible clinician. Exclusion criteria were acute issues requiring immediate lifesaving interventions, cardioversion, or defibrillation within the previous 24 hours, ST-segment elevation MI leading to immediate reperfusion therapy, women who were pregnant or breast feeding, or patients that were transferred from other facilities. Patients provided informed written consent, and the study was approved by the Institutional Review Board at Henry Ford Hospital, Detroit, Michigan. Research coordinators enrolled the patients, obtained a history from the patient, recorded the primary symptom at presentation, and reviewed the electronic medical record.

Baseline blood samples were collected in ethylenediamine tetraacetic acid tubes within 60 minutes of the completion of the presentation ECG in the ED. Additional samples were collected at 1 hour and 3 hours. The tubes of blood were centrifuged to obtain plasma and placed in a −80°C freezer within 1 hour of sampling. Samples were analyzed using the hs-cTnI Access assay (Beckman Coulter, Brea, CA) at Henry Ford Hospital. This hs-cTnI has a 99th percentile of 18.2 ng/L, a limit of blank of 0.077 ng/L, a limit of detection of 0.32 ng/L, and limit of quantification of 0.77 ng/L.[21] The 0/1-hour AMI algorithm that places patients in a rule-out, observation, or rule-in zone was evaluated. Patients in the rule-out zone had hs-cTnI <4 ng/L at 0 hour or <5 ng/L at 0 hour and a delta from 0 to 1 hour <4 ng/L. Patients in the rule-in zone had 0 hour ≥50 ng/L or delta at 1 hour ≥15 ng/L. Patients that did not meet the criteria for either the rule-in zone or rule-out zone were placed in the observation zone (Figure 1). The hs-cTnI values for the algorithm were determined in a prior study.[19]

### 0/1-hour algorithm with hs-cTnI

The determination of the final diagnosis of AMI was done using the hs-cTnT (Roche Diagnostics, Indianapolis, IN) and required at least 1 hs-cTnT >19 ng/L, which is the Food and Drug Administration approved 99th percentile for use in the United States.[22] There were 3 physicians involved in the determination of AMI: 2 board-certified cardiologists and 1 emergency physician. Two physicians reviewed the cases independently and classified the AMI as either Type 1 or Type 2. Only in the case of disagreement in the diagnosis of AMI (Type 1 or Type 2) between the initial 2 physicians was the case reviewed by the third physician for final adjudication. The reviewing physicians also classified all deaths at follow-up as either cardiac or noncardiac and interpreted all ECGs. The reviewing physicians had access to the electronic medical records, which included all testing done during the admission. The determination of AMI was done in accordance with the principles of the universal definition of MI.[16] The results of both the hs-cTnI and the hs-cTnT

were blinded to the responsible clinicians managing patients. At the time of this study neither hs-cTn assays were approved for use in the United States. The assay that was used clinically was the contemporary cTnI Ultra (Siemens Medical Solutions, Malvern, PA). The 99th percentile of the Siemens assay is 40 ng/L and any number above this was reported to the clinician.

Research personnel recorded the results of echocardiograms, stress tests, and coronary angiograms done during the study. The ordering of cardiac tests was left to the discretion of the responsible clinician. An echocardiogram was considered abnormal if there was any wall motion abnormality noted (focal or global). Reports of the stress tests were reviewed to classify the tests as positive, negative, or indeterminate. A coronary angiogram was considered abnormal if any blood vessel had a stenosis ≥70% or a left main stenosis ≥50%. Research personnel contacted the enrolled patients at 30 to 45 days and 12 to 18 months after discharge to determine if they experienced death, AMI, or a revascularization procedure (percutaneous coronary intervention [PCI] or coronary artery bypass grafting surgery [CABG]). Follow-up information was obtained from a telephone call and subsequent medical record review. If subjects or family members were not able to be reached by telephone, an electronic medical record review was completed. Also Ancestry.com Michigan obituaries was queried, and a Google search was used. Beckman Coulter financially supported the study. The authors are solely responsible for the design and conduct of the study, all study analyses, the drafting/editing of the paper, and its final contents.

### Statistical analysis

The baseline patient characteristics have been compared across the 3 algorithm zones using analysis of variance for numerical data, the chi-square test for nonsparse categorical data, and the Fisher exact test for sparse categorical data. Cardiac procedure status has been compared across the 3 algorithm zones using the chi-square test for nonsparse data and the Fisher exact test for sparse data. Resulting *P* values less than .05 have been considered statistically significant. All analyses have been performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC).

## Results

### Diagnostic/prognostic utility

From May 2013 to April 2015, there were 569 patients that qualified as eligible patients. There were missing hs-cTnI data in 17 patients leading to 552 patients in the final analysis. Baseline clinical characteristics, symptoms, vital signs, ECG findings, and home medications of patients in the rule-out, observation, and rule-in zones are shown (Table I). In general, patients in the rule-in zone, as compared to the rule-out zone, were older and had more comorbidities, such as hypertension, hypercholesterolemia, prior AMI, or coronary revascularization procedures. The final diagnosis during the initial ED/hospital presentation was AMI in 45 (8.2%) patients. In AMI patients that presented <3 hours after symptom onset (n = 15) the median hs-cTnI value at time 0 was 25.1 ng/L (interquartile range [IQR] 15.4-65.1 ng/L), as compared to the AMI patients that presented later (n = 30) median hs-cTnI 78.9 ng/L (IQR 24.1-458.0 ng/L; *P*= .037). Of the AMIs there was 1 ST-segment elevation MI (included as the patient was not recognized as such and did not receive immediate reperfusion therapy) and the rest were non-ST-segment MIs. There was good agreement between the 2 physicians determining AMI (kappa = 0.97; 95% confidence interval [CI] 0.92-1.00). In only 2 cases of AMI was there disagreement requiring a third physician to adjudicate the case. Within 30 to 45 days, there were 5 deaths (3 cardiac and 2 noncardiac), an additional 8 AMIs, and 23 revascularization procedures (20 PCIs and 3 CABGs).

Of the 270 patients in the rule-out category, there was only 1 AMI yielding a NPV of 99.6% (95% CI 98.0-100) and sensitivity of 97.8% (95% CI 88.2-99.9; Figure 2). The median time from presentation to baseline blood draw was 1 hour (IQR 0.8-1.1 hours), and the median time for presentation to the 1-hour blood draw was 2.0 hours (IQR 1.8-2.2 hours). The one AMI patient that was not identified by the rule-out algorithm was a 57-year-old male with typical symptoms of increasing chest pressure that was worsened by physical exertion. The patient reported continual symptoms for >24 hours prior to presentation. He underwent a PCI 1 month prior and had diffuse coronary artery disease (CAD). He was placed in the observation unit, and his cardiologist recommended to discharge the patient with an increase in his antianginal medications. He did not suffer death or recurrent AMI at 30 to 45 days. Of patients in the rule-out zone, 232 (85.9%) had an hs-cTnI <4 ng/L at presentation, while 38 (14.1%) required the 1-hour draw to rule-out. Of those in the rule-in group, there were 30/53 (56.6 %) that had an AMI yielding a positive predictive value (PPV) of 56.6% (95% CI 42.3-70.2) and specificity of 95.5% (95% CI 93.3-97.1). Of patients in the observation zone, there were 14 (6.1 %) with AMI (Figure 2). Of patients with hs-cTnI ≥50 ng/L at presentation, 23 (53.5%) had an AMI; of patients with a 1-hour increase of hs-cTnI ≥15 ng/L, 18 (81.8%) had an AMI (*P* = .025). In looking at MACE by the 3 zones (rule-out, observation, rule-in): the 30- to 45-day death/AMI rates by were 0.4%, 2.6%, and 7.5% (*P*= .003) and the 12- to 18-month all-cause mortality rates were 0.7%, 4.8%, and 7.5% (*P*= .005; Figure 2), respectively. The mortality rates and AMIs are cumulative over the 12- to 18-month period. The median follow-up time was 12.2 months (IQR 12.1-12.4 months).

**Table I.** Baseline clinical characteristics by the 3 zones

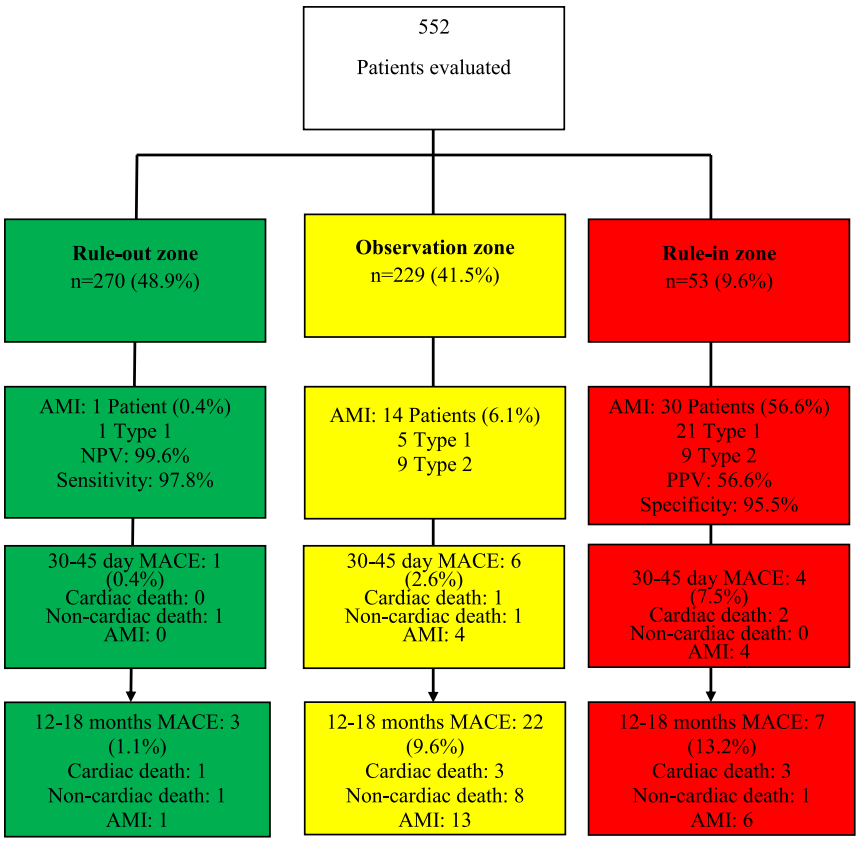
| | All patients (N = 552) | Rule-out (N = 270) | Observation (N = 229) | Rule-in (N = 53) | *P* value |
|---|---|---|---|---|---|
| Demographics | | | | | |
| Age, mean ± SD, years | 55.6 ± 11.1 | 53.0 ± 10.4 | 57.9 ± 11.2 | 59.2 ± 10.5 | <.001 |
| Male gender (%) | 286 (51.8) | 106 (39.3) | 145 (63.3) | 35 (66.0) | <.001 |
| Race, frequency (%) | | | | | |
| Caucasian | 90 (16.3) | 55 (20.4) | 23 (10.0) | 12 (22.6) | .007 |
| African American | 459 (83.2) | 214 (79.3) | 204 (89.1) | 41 (77.4) | |
| Other | 3 (0.5) | 1 (0.4) | 2 (0.9) | 0 (0.0) | |
| History, frequency (%) | | | | | |
| Hypertension | 448 (81.2) | 191 (70.7) | 209 (91.3) | 48 (90.6) | <.001 |
| Diabetes | 161 (29.2) | 71 (26.3) | 75 (32.8) | 15 (28.3) | .284 |
| Hypercholesterolemia | 273 (49.5) | 108 (40.0) | 133 (58.1) | 32 (60.4) | <.001 |
| Smoking | 205 (37.1) | 107 (39.6) | 76 (33.2) | 22 (41.5) | .262 |
| CAD | 199 (36.1) | 74 (27.4) | 95 (41.5) | 30 (56.6) | <.001 |
| Family history of CAD | 213 (38.6) | 88 (32.6) | 94 (41.0) | 31 (58.5) | <.001 |
| PCI | 125 (22.6) | 45 (16.7) | 57 (24.9) | 23 (43.4) | <.001 |
| CABG | 30 (5.4) | 7 (2.6) | 16 (7.0) | 7 (13.2) | .003 |
| Prior acute myocardial infarction | 163 (29.5) | 58 (21.5) | 80 (34.9) | 25 (47.2) | <.001 |
| Congestive heart failure | 132 (23.9) | 30 (11.1) | 78 (34.1) | 24 (45.3) | <.001 |
| Dialysis | 27 (4.9) | 1 (0.4) | 22 (9.6) | 4 (7.5) | <.001 |
| Presenting vital signs, mean ± SD | | | | | |
| Systolic BP, mm Hg | 144.5 ± 25.7 | 141.8 ± 22.1 | 147.2 ± 27.3 | 147.0 ± 33.3 | .049 |
| Diastolic BP, mm Hg | 85.3 ± 17.4 | 84.5 ± 15.1 | 85.9 ± 18.8 | 87.3 ± 22.1 | .452 |
| Pulse rate, beats/min | 83.6 ± 18.7 | 82.3 ± 17.5 | 84.2 ± 18.5 | 88.4 ± 24.5 | .078 |
| Electrocardiogram finding, (%) | | | | | |
| Atrial fibrillation | 19 (3.4) | 2 (0.7) | 14 (6.1) | 3 (5.7) | .003 |
| Left ventricular hypertrophy | 92 (16.7) | 24 (8.9) | 58 (25.3) | 10 (18.9) | <.001 |
| Left bundle branch block | 9 (1.6) | 0 (0.0) | 8 (3.5) | 1 (1.9) | .003 |
| Paced ventricular rhythm | 13 (2.4) | 1 (0.4) | 8 (3.5) | 4 (7.5) | .002 |
| ST-segment elevation ≥1 mm | 19 (3.4) | 10 (3.7) | 7 (3.1) | 2 (3.8) | .916 |
| ST-segment depression ≥1 mm | 23 (4.2) | 3 (1.1) | 13 (5.7) | 7 (13.2) | <.001 |
| T-wave inversion | 167 (30.3) | 40 (14.8) | 98 (42.8) | 29 (54.7) | <.001 |
| Within normal limits | 148 (26.8) | 114 (42.2) | 29 (12.7) | 5 (9.4) | <.001 |
| Creatinine levels | | | | | |
| Median IQR | 0.97(0.80-1.27) | 0.86(0.75-1.01) | 1.13(0.9-1.48) | 1.11(0.88-1.57) | <.001 |
| Home medications, frequency (%) | | | | | |
| Aspirin | 292 (52.9) | 118 (43.7) | 133 (58.1) | 41 (77.4) | <.001 |
| Anticoagulant | 48 (8.7) | 14 (5.2) | 30 (13.1) | 4 (7.5) | .007 |
| Diuretics | 137 (24.8) | 54 (20.0) | 63 (27.5) | 20 (37.7) | .011 |
| Angiotensin-converting enzyme inhibitor | 212 (38.4) | 84 (31.1) | 102 (44.5) | 26 (49.1) | .002 |
| Angiotensin-receptor blocker | 37 (6.7) | 13 (4.8) | 20 (8.7) | 4 (7.5) | 0.211 |
| Beta-blocker | 248 (44.9) | 78 (28.9) | 134 (58.5) | 36 (67.9) | <.001 |
| Calcium channel blocker | 137 (24.8) | 50 (18.5) | 71 (31.0) | 16 (30.2) | .004 |
| Nitrates | 127 (23.0) | 42 (15.6) | 65 (28.4) | 20 (37.7) | <.001 |

BP, blood pressure; CABG, coronary artery bypass graft; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; PCI, percutaneous coronary intervention.

## Stress testing, echocardiography, and coronary angiography

Those in the rule-in zone more commonly had a wall motion abnormality on their echocardiogram, an abnormal stress test with imaging, or required a revascularization procedure. Of patients in the rule-out zone, 95 (35.2%) received some form of stress testing, 22 (8.1%) had an echocardiogram, and 9 (3.3%) underwent coronary angiography (Tables II and III). For patients in the rule-out zone, the majority of stress tests 86 (90.5%) were normal and these patients were discharged. There were only 6 (6.3%) patients that were positive for ischemia and 3 (3.2%) patients that were nondiagnostic (no further testing done). Of the 6 patients with positive stress tests, 2 of them underwent CCTAs and 2 underwent coronary angiography with all 4 demonstrating normal coronary arteries. Only 1 of these patients had a mildly positive stress nuclear test finding, which prompted a cardiology consult. This patient had a recent coronary angiogram and medical management was recommended. There was 1 other patient that had an abnormal stress nuclear test and underwent coronary angiography, which demonstrated significant left main disease which led to a CABG surgery. This patient was a 65-year-old female with a history of diabetes mellitus type 2 and hypertension who presented with atypical chest pain.

**Figure 2**




Patient outcomes in the rule-out, observation, and rule-in zones. AMI, acute myocardial infarction; MACE, major adverse cardiac event; MI, myocardial infarction; NPV, negative predictive value; PPV, positive predictive value.

Characteristics of the 9 patients that had coronary angiography in the rule-out group are shown (Table III). Of these there were 5 patients (all with a known history of CABG or prior PCI) that went directly to coronary angiography based on the history without a stress test: 3 underwent PCI and with 2 medical therapy was advised. There were also 2 patients that underwent coronary angiography after a normal stress due to clinical suspicion: 1 was normal and 1 had obstructive CAD but was treated medically. All of the 4 revascularization procedures happened at the time of the index visit. Of the 22 patients in the rule-out group that had an echocardiogram, 1 demonstrated a wall motion abnormality. The echocardiogram demonstrated global hypokinesis with an ejection fraction of 40%, which was thought to be secondary to uncontrolled hypertension. Those in the rule-in group more commonly had a revascularization procedure. The median length of stay of patients in the rule-out zone that were discharged from the ED without stress testing or echocardiography was 5.7 hours (IQR 4.7-7.0 hours), which was significantly lower than those that had either a stress test or echocardiogram 26.6 hours (IQR 21.1-31.1 hours; $P < .001$).

## Types 1 and 2 AMIs and patient characteristics

There was a total of 27 Type 1 AMIs and 18 Type 2 AMIs (Figure 2). Patients with Type 1 AMIs more commonly had a history of PCI 18 (66.7%) when compared to those with Type 2 AMIs 4 (22%) ($P = .004$). There was no significant difference with other variables. There was a significantly higher percentage of Type 2 AMIs in the observation zone 9 (64.3%) when compared to the rule-in zone 9 (30.0%) ($P = .031$). All 27 Type 1 AMIs had chest pain as their primary presenting symptom while 14 (77.8%) of Type 2 AMIs had chest pain as the primary symptom. Patients with Type 1 AMI had higher median maximal hs-cTnI values over 3 hours of 214.6 ng/L (IQR 56.2-746.7) when compared to Type 2 AMIs at 73.4 ng/L (IQR 44.2-182.5), but this was not a significant difference ($P = .102$). Similarly, patients with Type 1 AMIs had a greater change from presentation to 1 hour 15.4 ng/L (IQR 2.6-54.4 ng/L) as compared to Type 2 AMIs at 10.6

**Table II.** Cardiac testing in the rule-out, observation, and rule-in zones

| | Rule-out zone (n = 270) N (%) | | | | Observation zone (n = 229) N (%) | | | | Rule-in zone (n = 53) N (%) | | | | *P* value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | Normal | Abnormal | Nondiagnostic | N | Normal | Abnormal | Nondiagnostic | N | Normal | Abnormal | Nondiagnostic | |
| Echocardiogram | 22 | 21 (95) | 1 (5) | 0 | 63 | 49 (78) | 14 (22) | 0 | 31 | 17 (55) | 14 (45) | 0 | .003 |
| Exercise stress test | 4 | 4 (100) | 0 | 0 | 1 | 0 | 1 (100) | 0 | 0 | 0 | 0 | 0 | .200 |
| Exercise echocardiogram or nuclear stress test | 36 | 33 (92) | 3 (8) | 0 | 14 | 10 (71) | 1 (7) | 3 (21) | 3 | 0 | 1 (33) | 2 (67) | <.001 |
| Pharmacological nuclear stress test or DSE | 55 | 49 (89) | 3 (5) | 3 (5) | 54 | 45 (83) | 5 (9) | 4 (7) | 10 | 4 (40) | 2 (20) | 4 (40) | .008 |
| Coronary angiogram | 9 | 4 (44) | 5 (56) | 0 | 11 | 2 (18) | 9 (82) | 0 | 25 | 5 (20) | 20 (80) | 0 | .326 |
| PCI or CABG | 4 (1.5) | | 5 (2.2) | | 14 (26.4) | | <.001 | | | | | | |

CABG, coronary artery bypass grafting; DSE, dobutamine stress echocardiogram; PCI, percutaneous coronary intervention.

ng/L (IQR 3.8-20.7 ng/L), but this was not significant (*P*= .749).

Although chest pain was the primary symptom in 41 (91.1%) of the AMI patients, the other 4 (8.9%) had a primary symptom of dyspnea or palpitations. In AMI patients, the median time from symptom onset to presentation was 10.2 hours (IQR 1.9-50.2 hours). There were 14 (31.1%) AMI patients that presented within 2 hours after symptom onset and 7 (15.6%) that presented within 1 hour of symptom onset. There were 27 patients with end-stage renal disease (ESRD) requiring dialysis, of which 4 had an AMI (2 in the observation zone and 2 in the rule-in zone). Only 1 of these 27 patients was in the rule-out zone. The PPV/specificity (56.6%/95.5%) for the rule-in zone was not significantly different if the dialysis patients were excluded from the analysis, 57.1%/95.7% (*P*= 1.000/.280).

For study patients 105 (19%) were not able to be contacted by telephone for follow-up at 30 to 45 days. Of these patients all had review of their electronic medical record. Of the patients that were not contacted by telephone, there was 1 cardiac death confirmed by a hospital admission. Of these 105 patients there were 77 (73%) that had no Henry Ford Hospital visits documented within the 30 to 45 days. However, at later follow-up of 12 to 18 months, there were only 14 (18%) of the 77 that did not have some documentation of an encounter in the medical record. Thus, ultimately there were 14/552 (2.5%) lost to direct follow-up. None of these 14 patients were found in a query of Ancestry.com Michigan obituaries.

## Discussion

To the best of our knowledge, this is the first study that has evaluated the diagnostic utility of noninvasive cardiac testing (echocardiography and stress testing) and described Type 1 and Type 2 AMIs in the context of the 0/1-hour AMI evaluation algorithm using a newer hs-cTnI assay in the ED. We report 3 key findings.

First, using a new hs-cTnI assay in a 0/1-hour algorithm demonstrated high diagnostic and prognostic utility. To date, there has only been 1 other publication to evaluate this particular hs-cTnI using the 0/1-hour algorithm.[19] The actual numbers used in these algorithms are assay specific and will depend on the specific manufacturer of the hs-cTn assay. The 0/1-hour algorithm had high NPV (99.6%) and sensitivity (97.8%) for AMI. These results are similar to other hs-cTn assays that have been studied in the 0/1-hour algorithm (sensitivities of 97.1%-97.6% and NPVs of 98.9%-99.2%).[13,14,23] In our study, there was only 1 AMI missed with the 0/1-hour algorithm. This patient was recognized based on the history alone as high risk and diagnosed with unstable angina. The 0/1-hour algorithm should not be used alone and should always be used in conjunction with the history and ECG. Those

**Table III.** Patients receiving a coronary angiogram in the rule-out zone

| Patient age and gender | Medical history | Symptoms | Stress test | Echocardiogram | Coronary angiogram | Revascularization |
|---|---|---|---|---|---|---|
| 50 male | No cardiac history or risk factors | Typical angina | No | No | Nonobstructive CAD | No |
| 61 female | Acute myocardial infarction with prior PCI/DES to LAD | Typical angina | No | No | Severe in-stent restenosis of LAD | PCI/DES to LAD |
| 60 male | CAD with prior PCI/DES to LAD | Typical angina | No | No | Single-vessel CAD | PCI/DES to LAD |
| 55 male | CAD with prior PCI/stent to RCA and circumflex | Typical angina | No | No | Patent stent to RCA and circumflex | No |
| 57 male | Uncontrolled Hypertension | Atypical chest pain | Positive | No | Nonobstructive CAD | No |
| 49 female | Hypertension, smoker, family history of CAD | Atypical chest pain | Positive | No | Normal coronaries | No |
| 65 female | Hypertension, diabetes mellitus type 2 | Atypical chest pain | Positive | No | 95% distal left main stenosis | CABG |
| 40 female | CAD known single vessel disease | Typical angina | Negative | No | Single-vessel CAD | PCI/DES to RCA |
| 76 female | CABG | Typical angina | Dobutamine stress echocardiogram cancelled due to severe pulmonary hypertension | Severe pulmonary hypertension | Occluded left internal mammary artery and saphenous vein graft, 100% stenosis LAD filled by collaterals | No |

CAD, coronary artery disease; CABG, coronary artery bypass grafting; DES, drug eluting stent; LAD, left anterior descanting artery; PCI, percutaneous coronary intervention; RCA, right coronary artery.

in the rule-out zone had an excellent prognosis. At 30 to 45 days, there were neither cardiac deaths nor additional AMIs. There was 1 noncardiac death. At 12 to 18 months, there was 1 additional death, which was cardiac. It should be noted the PPV for AMI for those in the rule-in zone was modest at 56.6%. However, we did demonstrate that an increase of hs-cTnI $\geq$15 ng/L at 1 hour was significantly more predictive of an AMI as compared to the single threshold of 50 ng/L at presentation.

Second, the majority of patients (145 [53.7%]) in the rule-out zone were recognized as low risk and sent home without further testing with a good 30 to 45 day prognosis. No cardiac deaths or subsequent AMI occurred in between hospital presentation and 30 to 45 days in any rule-out group patient. However, 126 (46.7%) went on to have an echocardiogram, stress test, or coronary angiography. There were 95 patients that underwent a stress test, of which 89 (93.7%) did not demonstrate ischemia. Of the 6 patients with an abnormal stress test, 4 were determined to be a false positive by either CCTA or coronary angiography. There was 1 patient with known CAD that had a mildly positive stress test where medical therapy was advised. There was 1 patient with a positive stress test that led to coronary angiography where severe left main disease was identified, which led to CABG. There were 5 patients (4 with history of CAD) that went to coronary angiography based on their history; 4 patients did not have stress testing and 1 had a negative stress test. Thus, in the entire group in the rule-out zone, a stress test significantly altered management in only 1 patient. In addition, only 1 of the patients in the rule-out zone had a wall motion abnormality on an echocardiogram.

The diagnostic utility of stress testing in low-risk patients as defined by the 0/1-hour algorithm is likely very limited. A large international study involving over 22,000 patients from 15 cohorts demonstrated that that those with very low hs-cTnI or hs-cTnT at presentation and very little change at 45 minutes to 2 hours were at very low risk for 30-day death or AMI.[24] Studies have shown there is an association between hs-cTnT values and coronary artery atherosclerotic burden by CCTA in stable outpatients. Those with normal CCTAs had very low hs-cTnT levels, while those with higher risk features, such as multivessel disease or remodeled plaques, had the highest values.[25,26] These findings suggest that stress testing might not be helpful in those with very low hs-cTn values. However, it should be noted stress testing was not investigated in these studies. Studies of low-risk patients being evaluated for possible AMI have shown the false-positive rate of different stress testing modalities ranged from 67% to 100%.[27,28] Most patients in the 0/1-hour rule-out zone likely can be discharged. Based on clinical judgment, there may be a minority that need further testing, such as stress testing, in those with known CAD, or CCTA in those without known CAD. However,

even if it is decided that patients need further testing, this likely can be done outpatient. There has been concern with the introduction of hs-cTn that there would be an increase in unnecessary stress testing and coronary angiography. A study of 2544 patients showed that the rate of coronary angiography was similar before and after the introduction of hs-cTn, as was the percentage of coronary angiographies that showed no obstructive disease. However, the use of stress testing was significantly lowered from 29% to 19% as was the time to discharge.[29] Greater than 40% of patients in our study in the rule-out zone were held for cardiac testing that added >20 hours to their length of stay. Thus, it is possible many in the rule-out zone do not need an extended stay for further cardiac testing and could be sent home for an out-patient evaluation. To prove this the algorithm would need to be prospectively implemented.

Third, there was a higher proportion of Type 2 AMIs in the observation zone 9 (64.3%) when compared to the rule-in zone 9 (30.0%). Type 2 AMIs had lower levels of hs-cTnI and also had a smaller change in hs-cTnI over 1 hour, although these differences were not statistically significant. Lower levels of cTn and less of a change over time in Type 2 AMIs has been reported in other studies.[30,31] These findings could be important in clinical cases when there is uncertainty about the type of AMI, which could impact the specific treatment plan and the disposition of the patient. Patients with Type 1 AMIs would likely best be managed on a cardiology service while the best disposition of Type 2 AMIs would depend on the underlying primary problem, such as sepsis or pulmonary embolism. We also noted that those with Type 1 AMIs more commonly had chest pressure or crushing chest pain as their primary symptom while those with Type 2 AMIs more frequently had dyspnea or dizziness, which has been noted in prior studies.[32]

Finally, we demonstrated the 0/1-hour algorithm to be an effective diagnostic tool in the manner it would be practically implemented in the ED. Prior studies of the 0/1-hour algorithm only included individuals that had chest discomfort as their presenting symptom.[13-15] However, atypical presentations of AMI exist, and many individuals are evaluated for possible AMI in EDs with symptoms other than chest discomfort such as dyspnea, syncope, or palpitations. There are reports that up to 33% of AMI patients do not have chest discomfort.[24] Patients were included in our study if there was some clinical suspicion for AMI irrespective of presenting symptoms. In the AMI group, 4 (8.9%) did not have chest discomfort as the presenting symptom. Also, there has been concern that the 0/1-hour algorithm may not perform as well in patients that present early after symptom onset as many studies did not include a large number of such patients. The European Society of Cardiology guidelines suggest the 0/1-hour algorithm not be used in patients that present <3 hours after symptom onset.[28] In our study, 14 (31.1%) of the AMI patients presented <2 hours after symptom onset and 7 (15.6%) presented within 1 hour of symptom onset. Although these numbers are modest, it is reassuring that the 0/1-hour algorithm performed well in these patients.

We included ESRD patients in the study and there was no difference in the specificity or PPV of the rule-in zone protocol with the inclusion of these patients. Although the number of ESRD patients was small, this suggests the algorithm could be used in such patients, but very few patients with ESRD would fulfill the rule-out protocol and require later hs-cTn measurements. A prior study evaluated a 0/1-hour algorithm in patients with renal dysfunction but not requiring dialysis.[33] This study found that using different cut-points for the rule-in did not significantly improve the diagnostic utility of the algorithm and recommended using the established algorithm. Since safety is the most important consideration in the use of the algorithm, it seems simpler and reasonable to apply the standard algorithm in those with ESRD with the realization that only a few will reside in the rule-out zone. Finally, over 80% of the patients were African American which distinguishes this analysis from other studies of the 0/1-hour algorithm where this population has been underrepresented.

## Limitations

This was a single-center trial in a US urban setting with a modest number of patients at 552. If this were a multicenter trial involving different communities and more patients, the results may have been different. The hs-cTnI assay used was applied retrospectively and was not known to the responsible clinicians. The algorithm should be prospectively validated with this assay. Of the AMI patients, only 7 (15.6%) presented within 1 hour of symptom onset. If there were a larger percentage of early presenters, the NPV may not have been as favorable. The number of AMIs was modest at 45. Finally, there were 14 (2.5%) we were not able to obtain any follow-up information at 12 to 18 months.

## Conclusion

We demonstrated that in a largely African American population evaluated for AMI in the ED the 0/1-hour algorithm using a hs-cTnI assay had high sensitivity for AMI and identified a population at low risk for death/AMI at 30 to 45 days. Noninvasive testing with echocardiography or stress testing had low diagnostic yield in patients in the rule-out zone. Patients in the rule-out zone could be considered for outpatient evaluation, which would significantly decrease the length of stay in the ED. Finally Type 2 AMIs more commonly were found in the observation as compared to the rule-in zone.

## Conflict of interest

The authors had total control of the data for independent analyses, interpretation, and writing. Dr. McCord has received research funding from Abbott Diagnostics, Roche Diagnostics, Beckman Coulter, and Siemens Healthineers; and has been a consultant to Roche Diagnostics, Siemens Healthineers, and Beckman Coulter. Dr. Cook has received research funding from Beckman Coulter, Roche Diagnostics, Critical Diagnostics, and Greiner Bio-One; and has been a consultant to Beckman Coulter and Roche Diagnostics. Dr. Miller has received research funding from Beckman Coulter, NeuMoDx, Gilead, Calcimedica, and BrainScope. Dr. Mueller has received research support from the Swiss National Science Foundation, the Swiss Heart Foundation, the Kommission fur Technologie und Innovation, the Stiftung fur Kardiovaskulare Forschung Basel, the University of Basel, Abbott, AztraZeneca, Beckman Coulter, Biomerieux, Brahms, Ortho Clinical Diagnostics, Roche, Siemens, Singulex, Sphingotec, and the University Hospital Basel; and has received speaker honoraria and/or consulting honoraria from Abbott, Amgen, AstraZeneca, Biomerieux, Boehringer Ingelheim, Bristol-Myers Squibb, Brahms, Cardiorentis, Novartis, Roche, Sanofi, Siemens, and Singulex. Dr. Nowak has been a consultant for Siemens Healthineers, Roche Diagnostics, Beckman Coulter, Ortho Diagnostics, and Abbott Diagnostics. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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